Zinc

Introduction

Zinc is an essential element that demonstrates a classic U-shaped dose-response curve in which adverse effects are associated with receiving either too little or too much zinc. Zinc deficiency resulting from inadequate dietary intake can lead to a variety of physiological and developmental impairments, as evidenced by areas of endemic hypogonadism and dwarfism in rural Iran (Cousins 1996; King and Keen 1999). Conditioned (secondary) zinc deficiency related to diseases, iatrogenic causes, impaired absorption, or excess zinc loss can also result in a variety of negative health effects.

Zinc is essential for the functions of numerous enzymes, including many involved in acid-base balance, amino acid metabolism, protein synthesis, and nucleic acid synthesis and function. For example, a zinc-dependent enzyme facilitates the conversion of food forms of folic acid (pteroylpolyglutamates) to free folic acid (pteroylmonoglutamate) to permit the body's utilization of food folates. Subsequently, the conversion of pteroylheptaglutamate to free folic acid is impaired with zinc deficiency. Experimental zinc deficiency has also been correlated with reproductive failure, loss of epidermal integrity, and immune dysfunction.

Safety Considerations

Zinc toxicity can occur either acutely or chronically. Acute zinc toxicity includes nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headache (Institute of Medicine [IOM] 2001). The acute effects of zinc excess typically result from ingesting gram quantities of zinc, which could occur by consuming 40 to 60 servings of a typical multivitamin that provides RDA levels of essential nutrients.

Chronic adverse effects of zinc excess are more subtle. The IOM set its UL value based on a clinical trial in which 60 mg of zinc produced an inhibition of copper-dependent superoxide dismutase. However, the researchers did not determine how much reserve functional capacity is

available for this enzyme and whether a small decrease in activity would have any relevant clinical impact. The IOM applied a UF of 1.5 to calculate an adult UL of 40 mg zinc per day.

Supplemental zinc has been shown to influence several biomarkers that may have clinical relevance in certain populations. Zinc supplements of 150 mg per day for 6 weeks have been shown to suppress lymphocyte stimulation response, thereby compromising immune function in healthy subjects (Chandra 1984; Greger 1994). Zinc supplements of 50 mg or more per day have been shown to decrease serum HDL cholesterol levels (Hooper et al. 1980; Freeland-Graves et al. 1982; Black et al. 1988). Total intakes of 60 mg of zinc decreased levels of copper (Fischer et al. 1984) and iron (Yadrick et al. 1989).

There are several medications that can interact with zinc, including antibiotics such as quinoline compounds and penicillamine, as well as several diuretics, such as hydrochlorothiazide. Zinc supplementation can interfere with the activity of medications, or in some cases medication can result in zinc depletion. A full discussion of drug-nutrient interactions is beyond the scope of this report, and individuals taking prescription medication should be advised to consult with their health care provider about potential drug-nutrient interactions.

Certain zinc–folic acid interactions are well documented (Butterworth and Tamura 1989). But the crucial issue is whether higher intakes of either zinc or folic acid may disrupt the bioavailability or function of the other and, if so, what the intakes associated with such effects are. Some reports of zinc–folic acid interactions suggest the possibility that supplemental folic acid could adversely affect zinc nutriture (Milne et al. 1984; Mukherjee et al. 1984; Simmer et al. 1987), but more recent reports have not uncovered any such interaction (Tamura et al. 1992; Kauwell et al. 1995). There are no Medline reports of high zinc intakes causing adverse effects through an antagonism of folic acid. Reports of anemia related to zinc intakes above 110 mg per day all describe the microcytic, hypochromic anemia associated with copper deficiency, a condition that could also interfere with iron utilization (Frambach and Bendel 1991; Gyorffy and Chan 1992; Summerfield et al. 1992; Greger 1994).

Certain chemical similarities cause zinc and copper to interact extensively (King and Keen 1999). Large quantities of zinc can interfere with copper uptake and modify copper binding, and

this effect has been used in treating Wilson disease, a defect that leads to excessive copper storage. Iron can interfere with zinc absorption when zinc is administered as a solution, but such interference has not manifested itself when zinc is consumed as part of a meal. Although high levels of calcium can also interfere with zinc absorption, the effect has no demonstrated practical importance.

Official Reviews

IOM (2001). The IOM found the adverse effects of excess zinc to include a suppressed immune response, decreased HDL cholesterol levels, and a reduced copper status. The IOM did not find adverse effects on human reproduction from excess zinc in their study. Of the various effects, the IOM selected the reduced copper status as the critical effect for deriving a UL for zinc. Specifically, the IOM used the data showing suppression of copper-dependent superoxide dismutase at 50 mg of zinc supplementation (Yadrick et al. 1989) to identify a LOAEL. Although no zinc intake from food was identified by Yadrick and coworkers, the IOM used population data to estimate a dietary zinc intake of 10 mg for the study. Thus, the IOM identified a LOAEL of 60 mg per day for total intake from all sources. A UF of 1.5 was selected to correct for uncertainty in extrapolation from a LOAEL to a NOAEL; the UF of 1.5 was judged to be adequate because reduced copper status is rare. Thus, the IOM UL for zinc is 40 mg per day for total intake from all sources.

European Commission, Scientific Committee on Food (EC SCF 2003). The EC SCF identified a NOAEL for zinc of approximately 50 mg per day. This NOAEL represents an overall conclusion based upon several studies. Although zinc intakes as low as 18.2 mg may decrease copper retention (Festa et al. 1985), this effect is readily corrected by adequate copper intake. Studies looking at the interplay between zinc and copper (Davis et al. 2000; Milne et al. 2001) indicate that copper balance and other indicators of copper status can be maintained when zinc intake is as high as 53 mg. No adverse effects were observed with 30 mg of supplemental zinc when dietary zinc was near 10 mg (Bonham et al. 2003a, 2003b). From these data collectively, the EC SCF identified its NOAEL of 50 mg of zinc and proposed a UF of 2 to derive a UL of 25 mg for total intake from all sources.

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM selected a LOAEL of 50 mg for supplemental zinc based on several studies (Black et al. 1988; Yadrick et al. 1989; Cunningham et al. 1994; Davis et al. 2000). To extrapolate from a LOAEL to a NOAEL, the EVM selected a UF of 2, resulting in a derived SUL of 25 mg per day for supplemental zinc. The total daily intake of 42 mg per day would not be expected to result in any adverse effects

CRN Recommendations

There are no known adverse effects of zinc at chronic supplemental levels of 30 mg per day (Bonham et al. 2003a, 2003b), and this level provides a substantial margin of safety below the levels associated with adverse effects (at least 50 mg of supplemental zinc). Therefore, 30 mg per day is identified as the CRN UL for supplements. Assuming a dietary zinc intake of 10 mg, the CRN UL for supplements is exactly compatible with the 40 mg IOM UL for total intake. The CRN value is only slightly higher than the 25 mg supplemental SUL set by the EVM.

Quantitative Summary for Zinc

CRN UL, supplemental intake	30 mg/day
IOM UL, total intake	40 mg/day
EC SCF UL, total intake	25 mg/day
EC supplement maximum	Not determined
EVM, guidance level	25 mg/day supplemental intake; 42 mg/day total intake

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